

**PCT**
**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**  
(Chapter I of the Patent Cooperation Treaty)  
(PCT Rule 44bis)

Applicant's or agent's file reference C1-A0510Y1P	<b>FOR FURTHER ACTION</b>		See item 4 below
International application No. PCT/JP2006/311575	International filing date ( <i>day/month/year</i> ) 09 June 2006 (09.06.2006)	Priority date ( <i>day/month/year</i> ) 10 June 2005 (10.06.2005)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA			

<p>1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p> <p>3. This report contains indications relating to the following items:</p> <table> <tbody> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </tbody> </table> <p>4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).</p>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input checked="" type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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Date of issuance of this report 11 December 2007 (11.12.2007)	
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## PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

TRANSLATION

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis,1)

		Date of mailing (day/month/year)
Applicant's or agent's file reference <b>C1-A0510Y1P</b>		<b>FOR FURTHER ACTION</b> See paragraph 2 below
International application No. <b>PCT/JP2006/311575</b>	International filing date: (day/month/year) <b>09.06.2006</b>	Priority date (day/month/year) <b>10.06.2005</b>
International Patent Classification (IPC) or both national classification and IPC		
Applicant <b>CHUGAI SEIYAKU KABUSHIKI KAISHA</b>		

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis,1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b(s)(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JPO	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

<b>WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY</b>		International application No. <b>PCT/JP2006/311575</b>
<b>Box No. I</b>	<b>Basis of this opinion</b>	
<p>1. With regard to the language, this opinion has been established on the basis of:</p> <p><input checked="" type="checkbox"/> the international application in the language in which it was filed</p> <p><input type="checkbox"/> the translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).</p> <p>2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:</p> <p>a. type of material</p> <p><input checked="" type="checkbox"/> a sequence listing</p> <p><input type="checkbox"/> table(s) related to the sequence listing</p> <p>b. format of material</p> <p><input type="checkbox"/> on paper</p> <p><input checked="" type="checkbox"/> in electronic form</p> <p>c. time of filing/furnishing</p> <p><input checked="" type="checkbox"/> contained in the international application as filed</p> <p><input type="checkbox"/> filed together with the international application in electronic form</p> <p><input type="checkbox"/> furnished subsequently to this Authority for the purposes of search</p> <p>3. <input type="checkbox"/> In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.</p> <p>4. Additional comments:</p>		

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY		International application No. PCT/JP2006/311575
Box No. IV	Lack of unity of invention	
<p>1. <input type="checkbox"/> In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> paid additional fees</li> <li><input type="checkbox"/> paid additional fees under protest and, where applicable, the protest fee</li> <li><input type="checkbox"/> paid additional fees under protest but the applicable protest fee was not paid</li> <li><input type="checkbox"/> not paid additional fees</li> </ul> <p>2. <input checked="" type="checkbox"/> This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.</p> <p>3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> complied with</li> <li><input checked="" type="checkbox"/> not complied with for the following reasons:</li> </ul> <p>"The special technical feature" of the subject matter of claim 1 relates to a method for stabilizing sc(Fv)<sub>2</sub> including a process of introducing a site-directed mutation. "The special technical feature" of the subject matter of claim 10 relates to sc(Fv)<sub>2</sub> whose Tm value is not less than 55°C.</p> <p>These inventions are not so linked as to form a single general inventive concept, since there is no technical relationship among those inventions involving one or more of the same or corresponding technical features.</p> <p>4. Consequently, this opinion has been established in respect of the following parts of the international application:</p> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> all parts</li> <li><input type="checkbox"/> the parts relating to claims Nos. _____</li> </ul>		

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY		International application No. PCT/JP2006/311575
Box No. V	Reasoned statement under Rule 43bis.I(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	
1. Statement		
Novelty (N)	Claims <u>1-13</u>	YES
	Claims _____	NO
Inventive step (IS)	Claims _____	YES
	Claims <u>1-13</u>	NO
Industrial applicability (IA)	Claims <u>1-13</u>	YES
	Claims _____	NO
2. Citations and explanations:		
Document 1: WO, 01-79494, A1 (Chugai Pharmaceutical Co., Ltd.), 25 October, 2001 (25.10.01)		
Document 2: WO, 02-33073, A1 (Chugai Pharmaceutical Co., Ltd.), 25 April, 2002 (25.04.02)		
Document 3: J. Immunol. Methods, 1999, Vol. 231, No. 1-2, pages 177 to 189		
Document 4: Biochemistry, 2003, Vol. 42, No.6, pages 1517 to 1528		
Document 5: Int. J. Cancer, 2003, Vol. 107, No. 5, pages 822 to 829		
Claims 1-13		
The subject matters of claims 1-13 do not appear to involve an inventive step in view of documents 1-5 cited in the ISR.		
Documents 1-3 describe modified antibodies comprising a single strand polypeptide containing two H chain V domains and two L chain V domains of a monoclonal antibody.		
Documents 4-5 describe a method for stabilizing scFv by introducing a site-directed mutation into the scFv.		
As for the subject matters of claims 1-13, it was a well-known technical problem before filing the application concerned that when producing various modified antibodies, stability of the antibodies is improved. In order to solve the problem, it was a well-known art to introduce a mutation such as amino acid residue substitution. Therefore, a person skilled in the art could have easily introduced a mutation such as amino acid residue substitution into the sc(Fv) <sub>2</sub> antibody in the inventions described in documents 1-3, referring to the descriptions in documents 4-5.		